REMARKS

Claims 1 – 2, 43 – 45 and 49 are pending in the application. Claims 50 and 51 are added. Accordingly, claims 1 – 2, 43 – 45 and 49-51 will be pending in the application following entry of this amendment.

Support for the addition of claims 50 and 51 is found throughout the original claims and the specification as originally filed. In particular, support for claims 50 and 51 is at least found, for example, in original claims 30 and 31, and at page 9, lines 10-11 of the filed specification. No new matter is added.

Interview Summary

At the outset, Applicants thank Examiner Huynh for taking the time to discuss the outstanding enablement and written description rejections with Applicants' representatives on April 5, 2011 (the "Interview"). Although no firm agreement was reached on these issues, Examiner Huynh provided helpful comments for responding further to the Final Office Action and for advancing the application. During the Interview, Examiner Huynh suggested entry of claims reciting targeted glycoconjugates made by a process comprising a β (1, 4) - galactosyltransferase I Y289 variant. Applicants' representatives submit herewith an amendment and response, incorporating the Examiner's suggestions, as discussed in the Interview, along with a Request for Continued Examination.

35 U.S.C. §112, first paragraph

Enablement

Claims 1-2, 43-45 and 49 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

Claims 1-2, 43-45 and 49 are directed to a glycoconjugate comprising a bioactive agent and a targeting compound (i.e., a glycoprotein, glycolipid or carbohydrate) joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.

The Examiner asserts that "the specification, while being enabling only for a targeted glycoconjugate comprising a specific bioactive agent as shown the specific anticancer agent

listed at pages 14 – 15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP-galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase for detection assays, **does not** reasonably provide enablement for (1) any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) compris(ing) a ketone group attached to the C2 position of the galactose ring" as claimed.

Applicants respectfully maintain their disagreement for reasons already made on the record in the response filed on February 11, 2011.

The invention as claimed is a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the targeting compound is a glycoprotein, glycolipid or carbohydrate, and wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. Claims 1, 2, and 49 are directed to a glycoconjugate (i.e., a compound), which is not limited to a recited use. Furthermore, Applicants have exemplified that CREB or bovine lens α-crystallin can be labeled using recombinant O-Glc-NAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase and the generation. This level of enablement is at least acknowledged by the Examiner at pages 4-5 of the Office Action. Therefore, Applicants respectfully submit that the claims are enabled according to the standard set forth in M.P.E.P. §2164.01(c).

In view of the disclosure and guidance provided by the application, the state of the art at the time the application was filed and the high level of skill in the art at the time the application was filed, Applicants submit that one skilled in the art would be able to practice the claimed invention using no more than routine experimentation.

That is, experiments using binding assays routine in the art can be used to test the binding specificity of any of the targeting compounds that have been labeled according to the methods of the invention, or clinical studies set up according to methods routine in the art can be used to obtain clinical data on a targeting compound labeled according to the methods of the invention. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214,

219 (CCPA 1976). Given the knowledge available (e.g., regarding the targeting compounds, clinical trials, etc.) at the time of the invention, it is especially true that undue experimentation is not required to determine these properties of the glycoconjugates of the invention.

Regarding the structure of the glycoconjugates of the invention, Applicants have demonstrated in the Examples the ability of GalT to label the peptide TAPTS(O-GlcNAc)TIAPG, which encompasses an O-GlcNAc modification site within the protein CREB. Applicants used wild-type GalT and showed that only partial transfer of the keto-sugar was observed by LC-MS, however when the Y289L mutant was used there was greater activity and complete conversion. (see page 40, line 14 – 22). Further, Applicants show that the same strategy can be used for the labeling of the O-GlcNAc glycosylated protein CREB (see, e.g. page 45, line 8 – 23). The specification at page 10, line 15 states, "the targeting compound (T)…is covalently bonded to a saccharide residue (S) with the use of a galactosyltranserfase enzyme, preferably beta-1,4-galactosyltransferase (GalT). In one embodiment of the invention, a modified saccharide (S) is covalently associated with the targeting compound with the use of a genetically engineered GalT, such as Y289L GalT (as discussed above). The targeting compound can be any naturally occurring glycoprotein, glycolipid or carbohydrate or can be engineered, through chemical or recombinant techniques. For example, if the targeting compound does not include a GlcNAc residue, the compound can be engineered, either through recombinant or chemical techniques known in the art, so as to include such a residue. Preferably, the targeting compound includes an N-acetylglucosamine (GlcNAc) residue."

It is respectfully submitted that the specification provides sufficient enablement for the glycoconjugates of the invention with regard to their structural properties. That is, no undue experimentation regarding structure is required to obtain the glycoconjugates of the invention, and one skilled in the art would be able to practice the claimed invention using no more than routine experimentation.

Taken together, the teachings of the specification and knowledge of one of skill in the art enables one of skill in the art to practice the full scope of the claimed invention without having to resort to undue experimentation. Applicants accordingly request that the rejection of claims 1-2, 43-45 and 49 alleging lack of enablement be reconsidered and withdrawn.

Nonetheless, and without acquiescing in any way to the Office's position, Applicants have added claims 50 and 51, which provide a glycoconjugate comprising a bioactive agent and a

targeting compound (i.e., a glycoprotein, glycolipid or carbohydrate) joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose and which further recites that the targeted glycoconjugate is made using a β (1, 4) - galactosyltransferase I variant (Y289L, Y289I, and Y289N). Applicants offer these claims in accord with the Interview on April 5, 2011, in an effort to advance the application. It is respectfully submitted that claims 50 and 51 are commensurate in scope with what the Examiner has indicated is enabled. Accordingly, Applicants respectfully request consideration and allowance of claims 50 and 51.

Written Description

Claims 1 – 2, 43 – 45 and 49 were rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully maintain their disagreement for reasons already made on the record in the response filed on February 11, 2011.

The present claims are directed to a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the targeting compound is a glycoprotein, glycolipid or carbohydrate, and wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. Additionally, the claimed invention is directed to use of the glycoconjugate in medical therapy.

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the invention had possession of the claimed invention (M.P.E.P. §2163.04 II.A.3(a)). To satisfy the written description requirement, there is no *in haec verba* requirement, and claims may be supported in the specification through express, implicit, or inherent disclosure (MPEP §2163). Furthermore, a patent specification need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

The measurement of binding specificity and structural features of glycoconjugates are described and, if any experimentation would be required, such experimentation would be routine to one skilled in the art. Targeting compounds are described in the specification at page 10 and page 18. Applicants provide a particular example of antibodies as a targeting compound at p. 20 of the specification. Further, targeting compounds were well known in the art as described above.

Moreover, binding specificity of glycoprotein, glycolipid or carbohydrate targeting compounds was known in the art at the time of filing. For example, antibodies were known in the art at the time of filing to be targeting compounds. In particular, monoclonal antibodies against tumor antigens were known in the art as cancer therapeutic agents at the time of filing. For example, clinical trials were conducted with various monoclonal antibody therapeutics, such as bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody that has been evaluated in Phase II and Phase II trials, and Ramaswamy et al. (Clin Breast Cancer. 2003 Oct;4(4):292-4, provided herein) describe in combination with doclataxel in women with advanced breast cancer. Vande Putte et al. (Ann Rheum Dis. 2003 Dec;62(12):1168-77, provided herein), evaluate the efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Carbohydrate based targeted therapeutics were also well known in the art. For example, insulin is a well known therapeutic. Poulsen et al. (Diabetes Care. 2003 Dec;26(12):3273-9, provided herein), test a combination therapy with insulin as part, rosiglitazone, and metformin to treat reduced insulin secretion and insulin resistance in skeletal muscle and liver in type 2 diabetes. Further, the anticancer compound doxorubicin was well known by one of skill in the art at the time of filing as a targeted anticancer compound. Numerous publications from the time of filing teach the use of doxorubicin in clinical trials (see, e.g. Anton et al., Clin Breast Cancer. 2003 Oct;4(4):286-91, provided herein).

Bioactive agents are described at pages 10 - 18. Further, bioactive agents were well known in the art. Further, it was known in the art at the time of filing that bioactive agents, such as those claimed, could be used to treat various diseases. For example, the Campbell et al. reference (Cancer Res September 1, 2006 66; 8707), provided herein, demonstrates that statins prevent breast cancer growth in vivo and in vitro. The Cascone et al. reference (Ann Oncol. 2006 Mar;17 Suppl 2:ii46-48), provided herein, summarizes the clinical evidence on the anticancer

activity of small molecule EGFR inhibitors in small cell lung cancer. Restivo et al. (Diabetes Care. 2006 Dec;29(12):2650-3), provided herein, teach botulinum toxin treatment for oropharyngeal dysphagia associated with diabetic neuropathy. Brennan et al. (N Engl J Med. 2006 Nov 9;355(19):1967-77), abstract provided herein, compare a rabbit antithymocyte polyclonal antibody or basiliximab, an interleukin-2 receptor monoclonal antibody, in renal transplantation graft rejection. Villa et al. (Br J Cancer. 2006 Dec 4;95(11):1459-66. Epub 2006 Nov 21), provided herein, show that a prophylactic quadrivalent HPV vaccine was effective through 5 years for prevention of persistent infection and disease caused by HPV 6/11/16/18.

Applicants have demonstrated that antibodies can be galactosylated with Y289L GalT having a chemical handle at the C2 position in Bioconjugate Chem. 2009, 20, 1228 – 1236 (provided herein). Applicants describe the utility of Y289L GalT to transfer a sugar residue with C2-keto-Gal (or GalNAz) from their UDP derivatives to the N-acetylglucosamine residue of glycoproteins or glycopeptides. (see, e.g. Figure 5 on page 1233). Moreover, Applicants teach that the conjugation technology is a viable method that can be used for detection and targeting therapies. (see, p.1229). In Bioconjugate Chem. 1009, 20, 1383- 1389 (provided herein), Applicants describe the biological activity of the described glycoconjugates. For example, Applicants describe C-terminal extended fusion polypeptides of recombinant scFv fusion proteins that are used as the acceptor substrate for human polypeptide-alpha-N-acetylgalactosaminyltransferase II that transfers either GalNAc or 2-keto-Gal from their respective UDP-sugars to the side-chain hydroxyl group of the Thr residue(s). The fusion scFv proteins with the modified galactose are then conjugated with a fluorescence probe, Alexa488, that carries an orthogonal reactive group. The fluorescence labeled scFv proteins bind specifically to a human breast cancer cell line (SK-BR-3) that overexpresses the HER2 receptor, indicating that the in vitro folded scFv fusion proteins are biologically active and the presence of conjugated multiple Alexa488 probes in their C-terminal end does not interfere with their binding to the antigen.

Thus, the originally filed specification shows Applicants were in possession of the claimed invention. Clearly, the art supports the various known targeting compounds and bioactive agents, as claimed and taught in the specification, as well as their use. Any person skilled in the art would recognize Applicants were in possession of the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection alleging lack of written description under 35 U.S.C. §112, first paragraph.

Once again, without acquiescing to the grounds for the rejection, but to advance the application, Applicants have added claims 50 and 51, which provide a glycoconjugate comprising a bioactive agent and a targeting compound (i.e., a glycoprotein, glycolipid or carbohydrate) joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose and which further recites that the targeted glycoconjugate is made using a β (1, 4) - galactosyltransferase I variant (Y289L, Y289I, and Y289N). Applicants respectfully submit that reciting the use of a β (1, 4) - galactosyltransferase I variant (Y289L, Y289I, and Y289N) clarifies the structure of the targeted glycoconjugate such that one skilled in the art would recognize Applicants' claimed invention. Accordingly, Applicants respectfully request entry and allowance of claims 50 and 51.

CONCLUSION

In view of the foregoing amendments and arguments, Applicants respectfully request reconsideration and withdrawal of all pending objections/rejections and allowance of the application with claims 1 - 2, 43-45, and 49-51 presented herein. If a telephone call with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number shown below.

Applicants submit this paper in response to the Office Action dated October 13, 2011, and the Advisory Action dated March 2, 2011, together with a Request for Continued Examination, a Petition for a Three-month Extension of Time, and the requisite fees based on large entity status. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter) to our Deposit Account No. 04-1105, under Order No. 65431(47992).

Dated: April 13, 2011

Respectfully submitted,

Electronic signature: /Elbert Chiang, Ph.D./
Elbert Chiang, Ph.D.
Registration No.: 60,325
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5502
Attorneys/Agents For Applicant